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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/896,692	06/29/2001	Sudhir Agrawal	47508.556CN2	1859

23483 7590 10/02/2003

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	18

DATE MAILED: 10/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

F10

Office Action Summary	Application No. 09/896,692	Applicant(s) Agrawal
	Examiner Jane Zara	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 9-7-03, 11-6-02 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-39 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-39 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on Jun 29, 2001 is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-39 are pending in the instant application.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 121 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 14-22, 29-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 21, line 4, and in claim 16, lines 8-9, it is unclear whether the phrase "set forth as SEQ ID NO: 5" refers to the conserved gag region or its complement. Appropriate clarification is requested.

Claims 16-30 and 34-36 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: No positive step is recited in the claims.

The metes and bounds of an oligonucleotide "specifically complementary" to nucleotides 324 to 345 of gag, in claim 1, line 2, and in claim 16, lines 6-7, cannot be determined. Appropriate clarification is requested.

In claim 6, lines 2-3, the phrase "four 3'-terminal ribonucleotides" appears twice. Appropriate correction is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating HIV-1 or HIV-2 infection in a mammalian cell in vitro comprising the administration of SEQ ID Nos: 1-5, does not reasonably provide enablement for a method of inhibiting proliferation of HIV-1 or HIV-2 in a mammal comprising the administration of an oligonucleotide specifically complementary to nucleotides 324 to 345 of a conserved gag region of the HIV-1 genome set forth as SEQ ID NO: 1, 2, 3, 4, or 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method of treating HIV1 or HIV2 infection in a mammal comprising the administration of a 21 nucleobase oligonucleotide that specifically targets nucleotides 324 to 345 of the gag region of HIV1 genome, whereby HIV1 or HIV2 proliferation is inhibited.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene

transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of treating or inhibiting proliferation of HIV1 or HIV2 in a mammal comprising the administration of a 21 nucleobase oligonucleotide that specifically targets nucleotides 324 to 345 of the gag region of HIV1 genome, whereby HIV1 or HIV2 proliferation is inhibited. The specification teaches the inhibition of HIV1 infection in mammalian cells in vitro comprising the administration of SEQ ID NO: 1. The specification also teaches the means of testing orally administered antisense oligonucleotides for in vivo stability and biodistribution in

mice. The specification fails to teach the treatment or prevention of proliferation of HIV1 or HIV2 in an organism comprising the administration of antisense One skilled in the art would not accept on its face the examples given in the specification of the in vitro inhibition of HIV1 using antisense as being correlative or representative of the successful treatment or inhibition of HIV1 or HIV2 proliferation in an organism in view of the lack of guidance in the specification and known unpredictability associated with predetermining the efficacy of antisense in treating an organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery, inhibition of HIV1 or HIV2 proliferation or treatment effects provided in an organism using antisense.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to a method of treating HIV1 or HIV2 infection in a mammal comprising the administration of a 21 nucleobase oligonucleotide that specifically targets nucleotides 324 to 345 of the gag region of HIV1 genome, whereby HIV1 or HIV2 proliferation is inhibited. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring HIV1 or HIV2 in an organism whereby viral proliferation is inhibited in vivo, and further that treatment effects are provided. Since the specification fails to provide any particular guidance for the inhibition of HIV1 or HIV2 proliferation in an organism comprising the administration of antisense, and since

determination of the factors required in vivo success is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claim 1 is rejected under 35 U.S.C. 102(a) or 102(e) as being anticipated by Cohen et al.

Cohen et al teach a 21 nucleobase synthetic oligonucleotide that is specifically complementary to nucleotides 324-345 of a conserved gag region of the HIV1 genome, and which comprises phosphorothioate internucleotide linkages (See SEQ ID NO: 7 of Cohen et al. See also col. 1-2 of Cohen et al).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al as applied to claim 1 above, and further in view of Baracchini et al.

The claims are drawn to a 21 nucleobase synthetic oligonucleotide that is specifically complementary to nucleotides 324-345 of a conserved gag region of the HIV1 genome, and pharmaceutical formulations thereof, which oligonucleotide comprises phosphorothioate internucleotide linkages, at least four 5' or 3' terminal ribonucleotides which flank deoxynucleotides, and which terminal ribonucleotides comprise 2'-O-methyl ribonucleotides.

Cohen et al is relied upon as cited in the 102 rejection above.

Cohen et al do not teach oligonucleotides further comprising at least four 5' or 3' terminal ribonucleotides which flank deoxynucleotides, and which terminal ribonucleotides comprise 2'-O-methyl ribonucleotides.

Baracchini et al teach antisense oligonucleotides comprising 5' and/or 3' terminal ribonucleotides, which ribonucleotides comprise 2'-O-methyl groups (See col. 6-7).

It would have been obvious to one of ordinary skill in the art to incorporate phosphorothioate internucleotide linkages, as well as terminal, 2'-O-methyl modified ribonucleotides into antisense oligonucleotides because Baracchini et al teach the incorporation of both phosphorothioate modifications and modified ribonucleotides into antisense oligonucleotides for enhancing oligonucleotide stability from exonucleases and enhancing target cell uptake of antisense. One of ordinary skill in the art would have been motivated to incorporate 2'-O-methyl modified ribonucleotides into the terminal positions of antisense oligonucleotides in order to enhance oligonucleotide stability, and one of ordinary skill in the art would have expected that such modified terminal ribonucleotides would enhance antisense stability and metabolic halflife, thereby making more antisense available for target gene binding. One of ordinary skill in the art would have been motivated to incorporate multiple (e.g. 1-4 residues) modified ribonucleotides into the 5' and/or 3'-terminal regions of the antisense oligonucleotides because these modifications have been taught to enhance stability of the antisense, and one of ordinary skill in the art would have expected that stability would be enhanced with increasing numbers of modified residues inserted onto the 5' and/or 3' termini.

Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ

October 1, 2003